

Epclusa[®] (sofosbuvir/velpatasvir) Coadministration with Carbamazepine

This document is in response to your request for information regarding Epclusa[®] (sofosbuvir/velpatasvir [SOF/VEL]) and coadministration with carbamazepine.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

PK DDI Evaluation

Based on the PK profile of each active ingredient within SOF/VEL and carbamazepine, a PK interaction would be predicted.^{1,2} Coadministration of these agents is expected to decrease the concentrations of SOF and VEL due to the induction of the P-gp drug transporter by carbamazepine, leading to a reduced therapeutic effect of SOF/VEL. Coadministration is not recommended. For more information about carbamazepine, please refer to its product labeling.²

SOF/VEL PK¹

DDI Mechanism		SOF	VEL
Drug Transporters	P-gp/BCRP	Substrate	Substrate/Inhibitor
	OATP1B1	N/A	Inhibitor
	OATP1B3	N/A	Inhibitor
	OATP2B1	N/A	Inhibitor
Drug Metabolizing Enzymes	CYP1A2	N/A	N/A
	CYP2B6	N/A	Substrate
	CYP2C8	N/A	Substrate
	CYP2C19/19	N/A	N/A
	CYP2D6	N/A	N/A
	CYP3A4	N/A	Substrate

Relevant SOF/VEL Label Information¹

The coadministration of SOF/VEL and carbamazepine is not recommended. Drugs that are inducers of P-gp and/or moderate to strong inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may significantly decrease plasma concentrations of SOF and/or VEL, leading to potentially reduced therapeutic effect of SOF/VEL.

Table 1: Changes in PK Parameters for Coadministered Drug in the Presence of SOF, VEL, or EPCLUSA^a

Coadministered Drug	Dose of Coadministered Drug (mg)	SOF Dose (mg)	VEL Dose (mg)	N	Mean Ratio (90% CI) of SOF, VEL, or EPCLUSA PK With/Without Coadministered Drug No Effect=1.00			
					C _{max}	AUC	C _{min}	
Carbamazepine	300 twice daily	400 single dose	ND	24	SOF	0.52 (0.43, 0.62)	0.52 (0.46, 0.59)	NA

NA = not available/not applicable, ND = not dosed

a. All interaction studies conducted in healthy volunteers.

Clearance of HCV infection with direct acting antivirals may lead to changes in hepatic function, which may impact safe and effective use of concomitant medications. Frequent monitoring of relevant laboratory parameters (INR or blood glucose) and dose adjustments of certain concomitant medications may be necessary. For more information, please refer to Section 7.3 of the SOF/VEL US Prescribing Information (Established and Potentially Significant Drug Interactions).

Literature Search

A literature search was conducted via Ovid MEDLINE, BIOSIS Previews, and Embase databases for studies published between 1946 and April 16, using the search terms the concomitant use of Epclusa (sofosbuvir/velpatasvir) with carbamazepine and related search terms. Relevant citations found consist of case reports and real-world experiences describing hepatitis C virus treatment in patients receiving enzyme-inducing antiepileptic drugs, including carbamazepine. These reports describe patient outcomes under specific clinical circumstances; however, the data are limited in scope.

Boyle A, Marra F, Boothman H, et al. Coadministration of hepatitis C direct-acting antivirals and enzyme-inducing antiepileptic drugs: real-world experience from a multi-centre case series. *J Hepatol.* 2023;78(Suppl 1):S1202.

Marcos-Fosch C, Cabezas J, Crespo J, et al. Anti-epileptic drugs and hepatitis C therapy: real-world experience. *Journal of Hepatology.* 2021;75(4):984–985.

Patel S., Moser A., Domingo H. Sustained virologic response in DAA-treated HCV patients on anti-epileptic drugs. *J. Hepatol.* 2023;79(3):e121-e123. doi:10.1016/j.jhep.2023.05.018

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Rodriguez-Reyes M., Sotoca J.M., Soy-Muner D. Successful Sofosbuvir/ Velpatasvir treatment in a hepatitis C patient receiving chronic antiepileptic therapy: a case report. SUCCESSFUL Euro. J. Hosp. Pharm. Sci. Pra. 2022;29(SUPPL 1):A46.

Yin J., Hill L., Mansour M., Collier S., Barman P. Successful treatment of hepatitis C virus infection in patients on anti-epileptics or mood stabilizers using pharmacokinetic enhancers. Br. J. Clin. Pharmacol. 2023;89(6):1891-1895.

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Novartis Pharmaceuticals Corporation, TEGRETOL® (carbamazepine USP) Chewable Tablets, Suspension, TEGRETOL®-XR (carbamazepine extended-release tablets). US Prescribing Information. East Hanover, NJ.

Abbreviations

BCRP=breast cancer
resistance protein
DDI=drug-drug interaction

OATP=organic anion
transporting polypeptide
P-gp=P-glycoprotein
PK=pharmacokinetic(s)

SOF=sofosbuvir
VEL=velpatasvir

Product Label

For the full indication, important safety information, and Boxed Warning(s), please refer to the Epclusa US Prescribing Information available at:

http://www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎ 1-866-MEDI-GSI (1-866-633-4474) or 🌐 www.askgileadmedical.com

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🌐 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉ MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🌐 www.accessdata.fda.gov/scripts/medwatch

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